Evaluation of Bethesda System in Cytopathological Diagnosis of Thyroid Nodule and its Histopathological Correlation

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Abstract

Introduction: Fine needle aspiration cytology (FNAC) is an efficient, cost effective and safe out-patient procedure in diagnosis of thyroid nodules. With the advent of Bethesda system of reporting thyroid FNAC, the procedure has obtained even more standardization, reproducibility, predictive value and all in all, greater clinical significance.

Aim: The aim of this study was to assess the effectiveness of FNAC thyroid reported under Bethesda guidelines by comparing the preoperative cytological diagnoses with the postoperative histopathological diagnoses.

Methods: In this study, FNAC of 768 patients of clinically palpable thyroid swelling were evaluated and classified according to the Bethesda system. 188 patients of this group underwent surgical management and histopathological diagnosis was obtained in them. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNAC reported under Bethesda system were obtained by comparing the cytological and histopathological diagnoses.

Results: The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNAC came out to be 83.2%, 63.3%, 74.3%, 74.6% and 74.4% respectively.

Conclusion: In our study, FNAC reported under Bethesda system came out to be a highly efficient tool in diagnosis of thyroid nodules. However, addition of more advanced methods like immunocytochemistry and molecular techniques can further increase this efficacy especially in the groups diagnosed as Atypia of undetermined significance/Follicular lesion of undetermined significance, Follicular neoplasm/Suspected for follicular neoplasm and Suspected for malignancy.

Keywords: Thyroid, Bethesda System, FNAC, Histopathology

Access this article online	
Quick Response Code:	Website: www.innovativepublication.com
	DOI: 10.5958/2394-6792.2016.00045.4

Introduction

Thyroid lesions are very frequent with the annual incidence rate of 2-6%.[(1)] Palpable thyroid nodules are more common in women than men with a sex ratio ranging from 1.2:1 to 4.3:1.[(2,3)] Clinical symptoms vary from person to person ranging from mere cosmetic issue to both hypo and hyperthyroidism, compression effect on trachea or oesophagus as well as increased potential to give rise to a malignant lesion.[(4)] Therefore, the accurate evaluation of a thyroid nodule as to understand whether it is benign or malignant is of utmost importance. No single diagnostic procedure like X-ray, USG, scintigraphy or suppression therapy is enough to make this differentiation single handed. Fine needle aspiration cytology (FNAC) is an efficient, cost effective and safe out-patient procedure in this regard which is in use for more than 60 years now.[(5)] With the advent of Bethesda system of reporting thyroid FNAC, the procedure has obtained even more standardization, reproducibility, predictive value and all in all, greater clinical significance.

In this study, the effectiveness of FNAC thyroid reported under Bethesda guidelines was evaluated by comparing the preoperative cytological diagnoses with the postoperative histopathological diagnoses.

Materials and Methods

A retrospective study of 768 cases of clinically diagnosed thyroid swelling was carried out in the Department of Pathology of our hospital between June 2013 and June 2015. Cytological aspirate of all the cases were evaluated. Cytological and histopathological diagnoses were correlated in 188 cases who had undergone surgical excision after FNAC.

Cytological evaluation was based on Bethesda classification. After careful and thorough examination of the alcohol fixed and MGG stained aspirate smears, FNAC results were classified into 6 groups:

1. Nondiagnostic/Inadequate
2. Benign (consisting of goitre and thyroiditis)
3. Atypia of undetermined significance (AUS)/ Follicular lesion of undetermined significance(FLUS)
4. Follicular neoplasm (FN)/ Suspicious for follicular neoplasm (SFN)
5. Suspicious for malignancy (SFM)
6. Malignant

After exclusion of the non-diagnostic results, cytological diagnoses were classified as positive and

negative. Benign results were taken as negative whereas AUS/FLUS, FN/SFN, SFM and malignant cytological diagnoses were considered as positive.

The sensitivity and specificity of cytological diagnosis were evaluated on the basis of histopathological correlation. Patients with negative cytological diagnosis but later diagnosed as cases of Carcinoma or follicular adenoma on histopathological examination were considered as false negative whereas patients with positive cytological diagnosis but later diagnosed as goitre or thyroiditis were taken as false positive.

Comparing the cytological and histopathological diagnoses, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNAC were calculated. Those having non-diagnostic/inadequate FNAC were excluded from the study.

All statistical calculations were performed using SPSS(IBM SPSS Statistics for Windows, Version 22.0,©1989,2013, SPSS Inc. an IBM Company). Chi-square test and Student t-test were performed wherever applicable. A p value of <0.05 was taken as statistically significant.

Results

Out of 768 patients, 592 were female (77.08%) and 176 were male (22.92%). The mean age was 39.37±14.97 years with female to male ratio of 3.36:1. Male patients had significantly higher mean age than their female counterparts (41.47 and 38.75 years respectively, *P=0.03*). Majority of the cases presented between 3rd to 5th decades in life (67.32%). Highest incidence was found in 40-50 years age group (25.52%) followed by 30-40 years age group (24.74%) as shown in Table 1.

Table 1: Age distribution of cases subjected to cytologic evaluation

Age group (in years)	No. of cases	Percentage
0-10	15	1.95%
10-20	44	5.73%
20-30	131	17.06%
30-40	190	24.74%
40-50	196	25.52%
50-60	102	13.28%
60-70	60	7.81%
70-80	23	2.99%
80-90	7	0.91%

On FNAC, when classified as positive, negative and non diagnostic, 43.75% cases came out to be negative, 47.14% were positive and 9.11% were non diagnostic. The detailed cytologic distribution is shown in Table 2. Gender wise distribution gave 59.06% positive rate for males and 49.52% positive rate for females, (*P=0.03),* when the non-diagnostic cases are excluded [Table 3]. The cases with diagnosis of AUS/FLUS, FN/SFN and suspected for malignancy constituted 16.66% of the total study population.

Table 2: Distribution of Cytological diagnoses of 768 cases

Non diagnostic	70
Benign	336
AUS/FLUS	63
FN/SFN	23
SFM	42
Malignancy	234
Total	768

Table 3: Gender wise distribution of cytologically positive and negative cases excluding the non-diagnostic ones

Sex	Positive	Negative	Total
Male	101	70	171
Female	261	266	527
	362	336	698

Out of the 768 cases, 188 cases were operated and histopathological correlation was made after careful evaluation of the H & E stained slides. Among those, 85 cases (45.21%) came out to be benign and 103 cases (54.79%) were diagnosed as malignant. No significant gender wise difference was found between the malignant cases. The histopathological diagnoses are summarized in Table 4.

Table 4: Distribution of Histopathological diagnoses of 188 cases

Thyroglossal cyst	12
Colloid goiter	40
Lymphocytic thyroiditis	15
Granulomatous thyroiditis	18
Follicular adenoma	20
Follicular carcinoma	33
Papillary carcinoma	42
Anaplastic carcinoma	5
SCC	3
Total	188

When compared with previous cytological findings, malignancy was detected in 25% of the previous non diagnostic group, 25.4% of the previous benign group, 46.2% of the previous AUS/FLUS group (Fig. 1), 50% of the FN/SFN group, 70.8% of the suspected for malignancy group and 89.7% of the previous malignant group (Fig. 2 and 3). Comparison of cytological and histopathological findings is shown in Table 5.

Table 5: FNAC and Histopathological correlation

	No. of cases	Histological correlation available	Thyroglossal cyst	Colloid goitre	Lymphocytic thyroiditis	Granulomatous thyroiditis	Follicular adenoma	Follicular carcinoma	Papillary carcinoma	Anaplastic carcinoma	SCC
Non diagnostic	70	8	0	5	0	1	1	0	1	0	0
Benign	336	67	12	22	9	7	6	5	4	1	1
AUS/FLUS	63	13	0	6	1	0	4	1	1	0	0
FN/SFN	23	18	0	3	3	3	2	6	1	0	0
SFM	42	24	0	2	1	4	1	5	10	1	0
Malignancy	234	58	0	2	1	3	6	16	25	3	2
Total	768	188	12	40	15	18	20	33	42	5	3

Histological examination revealed 6 follicular adenoma, 5 follicular carcinoma, 4 papillary carcinoma, 1 anaplastic carcinoma and 1 SCC in cases which were reported benign cytologically. These cases were taken to be false negative. 6 cases of goitre and 1 case of thyroiditis were diagnosed histologically among the previous AUS/FLUS group (Fig. 4). 3 cases each of goitre, lymphocytic thyroiditis and granulomatous thyroiditis were found out in the previous FN/SFN group. Cases which were reported cytologically as suspected for malignancy and malignancy revealed 2 cases of goitre each and 5 and 4 cases of thyroiditis respectively when histological correlation was made. All these cases were considered as false positive cases. In this study, excluding the non diagnostic cases, 16.11% were false positive and 9.44% were false negative.

Statistical analysis showed the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNAC to be 83.2%, 63.3%, 74.3%, 74.6% and 74.4% respectively.

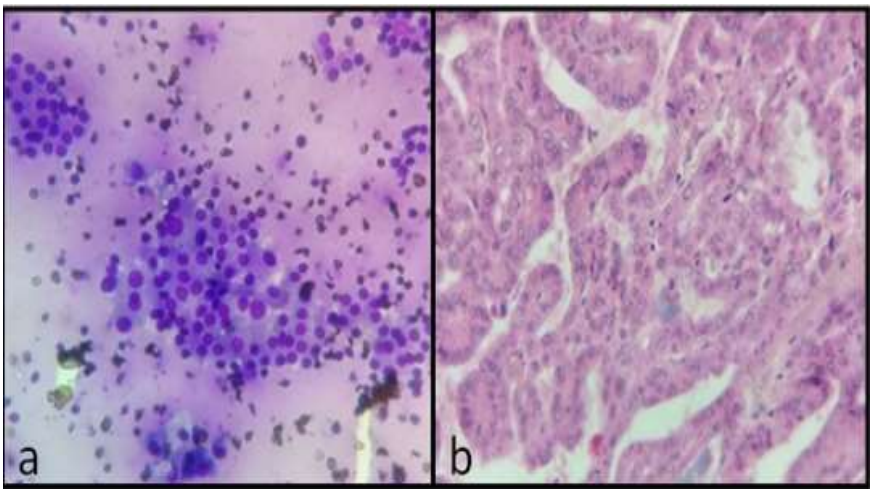

Fig. 1: (a) Case was diagnosed as atypia of undetermined significance due to mild nuclear pleomorphism and overlapping tendency of the cells (MGG, x400). (b) Histopathology section of the same case shows features of papillary carcinoma (H & E, x100)

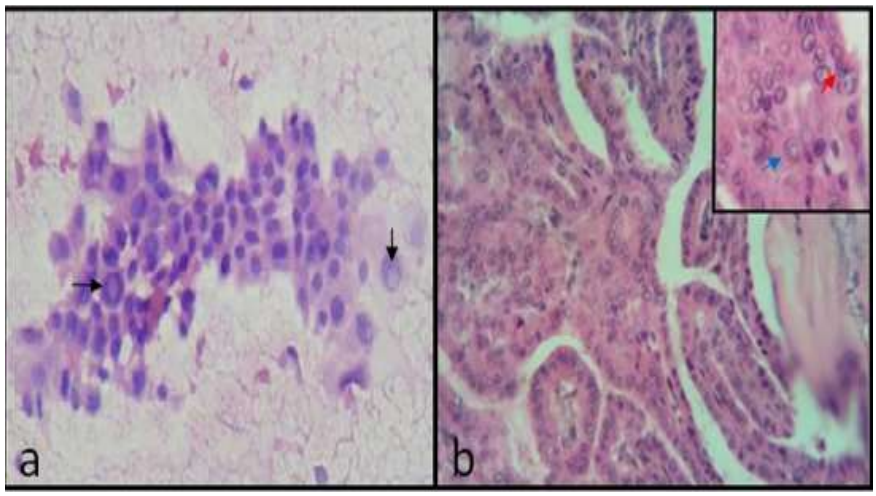

Fig. 2: (a) Case was diagnosed as papillary carcinoma due to prominent papillary arrangement & presence of intranuclear cytoplasmic inclusions (arrow) (MCG, x400). (b) Histopathology section of the same case confirmed the diagnosis. Insent shows nuclear grooving (red arrow) & intranuclear cyoplasmic inclusion (blue arrow). (H & E, x100)

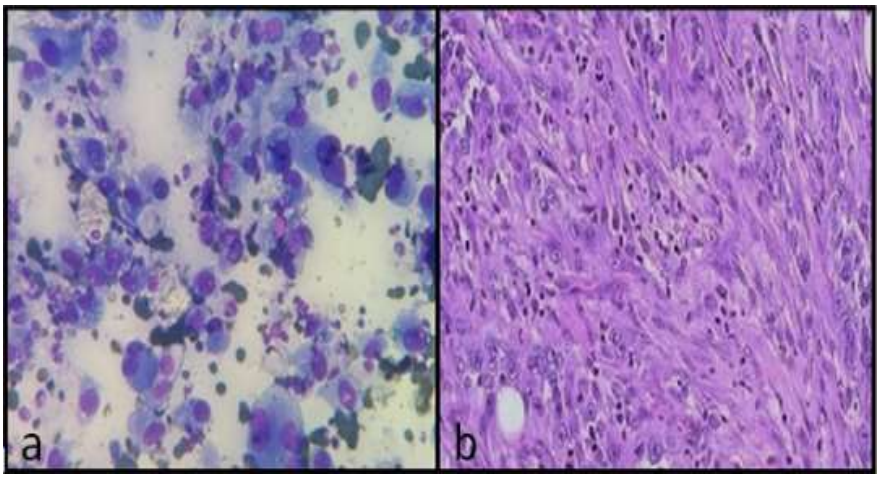

Fig. 3: (a) Case was diagnosed as anaplastic carcinoma (MGC, x400). (b) Histopathology section of the same case confirmed the diagnosis (H & E, x100)

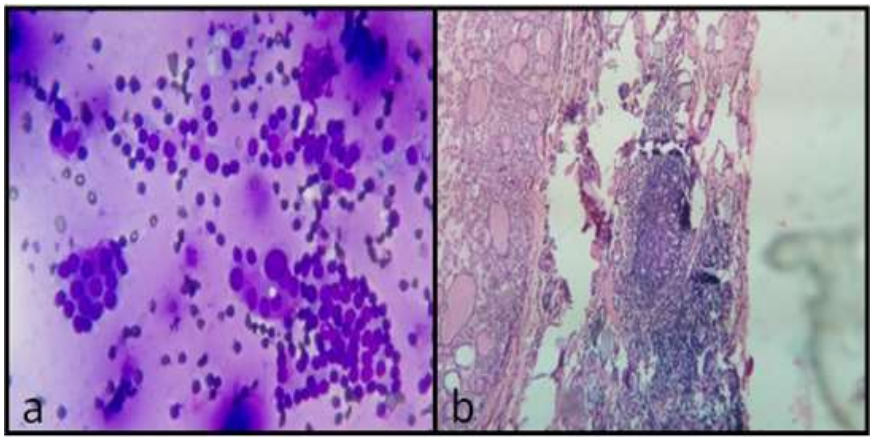

Fig. 4: (a) Case was diagnosed as atypia of undetermined significance due to presence of mild atypia, not enough to put it any other category (MGG, x100). (b) Histopathology section of the same case shows features of lymphocytic thyroiditis (H & E, x100)

Discussion

Thyroid malignancies constitute 1% of all cancers and are responsible for 0.5% of all cancer related deaths worldwide.[4] The slow rate of progression and relatively less aggressive course of thyroid cancers call for early detection of thyroid malignancies for better treatment outcome and longer survival as well as better quality of life for the patients.

FNAC is considered as one of the gold standard primary investigations for thyroid nodules. First used by Martin and Ellis way back in 1930s[6], as of now, each year more than millions of thyroid aspirations take place worldwide.[7] The procedure not only is cost effective and less complicated but also yields high diagnostic value. Widespread use of FNAC has reduced unnecessary operative interventions by about 25-50% while increasing the proportion of malignant diagnosis in patients who are operated.[8]

Published studies report the sensitivity and specificity of FNAC to diagnose thyroid malignancies to range between 65%-98% and 73%-100% respectively.(9–12) In our study, we found the sensitivity, specificity and accuracy to be 83.2%, 63.3% and 74.4% respectively. A comparison of our study with previous studies is given in Table 6.

Table 6: Comparison with other studies

Study	No. of cases	Sensitivity	Specificity	Accuracy	Positive Predictive Value	Negative Predictive Value
Al Sayer *et al.* [20]	70	86%	93%	92%	80%	96%
Bouvet *et al.* [21]	78	93.5%	75%	79.6%	85.3%	88.2%
Afroze *et al.* [22]	170	61.9%	99.31%	94.58%	92.86%	94.74%
Ko *et al.* [23]	207	78.4%	98.2%	84.4%	99%	66.3%
Cusick *et al.* [24]	283	76%	58%	69%	72%	64%
Muratli *et al.* [25]	126	87.1%	64.6%	77.3%	76.1%	79.5%
Present study	188	83.2%	63.3%	74.4%	74.3%	74.6%

Major reason behind the highly variable outcome of sensitivity and specificity among different studies is the introduction of AUS/FLUS category in the Bethesda classification, which covers all the lesions having architectural derangement and/or nuclear atypia but not enough to be put into any other category, making the diagnosis a highly subjective one. Moreover, some authors define AUS/FLUS, FN/SFN and SFM cases as to be of "intermediate category".[9,13] In our study, we have taken those as to be of positive category, constituting about 16.7% of our cases.

Published literatures report the rate of non diagnostic aspirations to be between 1.6% and 20%.[9,10,14,15] In our study, the non diagnostic cases constituted 9.11%, which is below 10%, as suggested by Ali *et al.*[15] The non diagnostic diagnoses are mostly due to sclerotic nodules or secondary calcification or cystic degeneration over a previous pathology.

In previous studies, the rate of false positive and false negative cases ranged in between 1%-7% and 1%-11.6% respectively,[9,10,12,16] while our study yielded 9.44% false negative and 16.11% false positive cases. Most common reason behind the false positive cases was nodular hyperplasia with numerous papillary structures. In our study, these cases were mostly diagnosed cytologically as AUS/FLUS or SFM. Again, follicular adenomas and well differentiated follicular carcinomas cannot be differentiated cytologically. Such conditions may give rise to false positive results.[14,17] False negative results were due to needling of adjacent benign areas in cases of malignancy. Multiple aspiration from different areas of the nodule may bring more accuracy to the cytological diagnosis.

The significant higher number of malignant cytology in males may be due to significantly higher mean age in male patients. This is in conjunction with previous studies.[2,18,19]

Conclusion

In conclusion, the findings of our study are consistent with that of published literature. "AUS/FLUS", "FN/SFN" and "SFM" group constitute a major proportion in our study group. In accordance with previous studies and with rapidly emerging knowledge on the above mentioned categories, we believe that addition of molecular techniques with the routine cytological procedure can open a new horizon on the diagnosis of thyroid pathology and cut short unnecessary surgeries to a bare minimum in near future.

Acknowledgements

The authors deny any conflicts of interest related to this study.

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